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REMARKS

This Amendment is being filed in response to the Office Action mailed from the U.S. Patent and Trademark Office on July 11, 2003, in which claims 1-15 and 35-65 were rejected. With this Amendment, claims 5 and 6 are canceled and claims 1, 7, 8, 12-14 and 53 are amended. As such, Applicant respectfully requests reconsideration and allowance of pending claims 1-4, 7-15 and 35-65.

The Final Office Action of July 11, 2003, rejected claims 1-15 and 35-65 under 35 U.S.C. §103 as being obvious under various combinations of U.S. Patent No. 6,103,518 to Leighton, U.S. Published Patent Application 2002/0132246 to Kallioniemi et al., a publication of Irving et al. (J of Clin. Path. (1996)49:258-259), and a publication of Goldsworthy et al. (Mol. Carcinog (1999)25(2):86-91). With this Amendment, the Applicant has amended independent claims 1 and 12 to include the limitation of a microarrayer comprising a cooling chamber—an element not disclosed, suggested, or taught in any of the cited references. The addition of the cooling chamber to the microarrayer provides a novel solution for the difficulties of utilizing a frozen sample with a tissue microarrayer (i.e., maintaining a frozen sample in a frozen condition during a coring process). The cited references, alone or in combination, **DO NOT** discuss these difficulties; more importantly, the cited references **DO NOT** provide, disclose, or suggest a solution to these difficulties which would render the Applicant's invention obvious. With this Amendment, Applicant respectfully requests reconsideration and allowance of pending claims 1-4, 7-15 and 35-65.

Leighton in view of Irving et al. and/or Goldsworthy et al.:

The Office Action of July 11, 2003 rejected claims 1-15 and 35-65 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,103,518 to Leighton, in view of Irving et al. (J of Clin. Path. (1996) 49: 258-259), stating:

> Leighton teaches a method for constructing tissue microarrays (also referred to as "tissue Chips") comprising,
>
> "taking samples from a series of donor tissues, one at a time, using a hollow, preferably needlelike, donor punch and placing each sample sequentially in a recipient of complementary shape in a recipient material by a recipient punch, thereby forming an array of tissues in the recipient block. Each punch comprises a punch tube and an

> associated stylet guided within the diameter approximating that of the donor punch inner diameter, and is dimensioned for sliding within the punch tube. The process of forming a hole in a recipient material such as paraffin, taking a sample of tissue from a donor specimen, and planting this sample in the hole in the recipient material, is repeated until a tissue array is formed comprising hundreds of tissue samples arranged in assigned locations in the recipient material. (col. 7). (Office Action Page 2-3).

Additionally, the Office Action states:

> Leighton teaches that the tissue samples are embedded in a block of paraffin or other embedding material. Leighton does not specifically teach the use of frozen embedding material.
>
> However, Irving teaches that storing pathological tissue or cell specimens in OCT embedding material (i.e., a frozen embedding material) "permits retrospective analysis of RNA from small amounts of stored pathological samples" (see abstract). In other words, Irving teaches that embedding samples in OCT embedding material produces high quality RNA (i.e., RNA is not likely to get degraded in OCT, as it would in paraffin embedding material) (pg. 258).
>
> In view of the teachings of Irving, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Leighton so as to have embedded tissue and/or cell samples in OCT embedding material, in order to have achieved the benefit of providing a higher quality RNA, which would help obtain better results when analyzing the tissue and/or cell samples in subsequent molecular analysis (such as expression analysis). (Office Action: Page 3-Page 4).

With this response, the Applicant has amended independent claim 1 to include the subject matter of canceled dependent claims 5 and 6. Further, the Applicant has amended independent claim 1 and independent claim 12 to disclose "A method for preparing a microarray of frozen tissue and/or cell samples comprising the steps of: ... providing a tissue microarray comprising a cooling chamber." Neither Leighton nor Irving et al. disclose or suggest a cooling chamber to maintain the tissue and/or cell sample in a frozen condition. Further, neither Leighton nor Irving et al. disclose, teach, or suggest any method of adapting a tissue microarrayer to overcome the difficulties of utilizing a frozen material (i.e., maintaining the sample in a frozen condition throughout the coring process). As such, amended independent claim 1, independent claim 12, and all depending claims overcome the Office Action's §103 rejections as the cited references do not disclose or suggest the element of a cooling chamber. The Applicant respectfully requests reconsideration and allowance of pending claims 1-4, 7-15 and 35-65.

The Applicant has disclosed a tissue microarrayer which has been adapted to be utilized with frozen embedding material. Standard tissue microarrayers are designed to be capable of being used with paraffin or an equivalent embedding material. Utilizing these standard microarrayers with a frozen embedding material has resulted in difficulty such as maintaining the sample in a frozen condition throughout the coring process and designing a coring needle and stylet capable of being used with the frozen material. To solve these difficulties, the Applicant has disclosed "A method for preparing a microarray of frozen tissue and/or cell samples comprising the steps of: ... providing a tissue microarray comprising a cooling chamber" (as claimed in amended independent claim 1 and amended independent claim 12). The cited references **DO NOT** discuss, teach, disclose or suggest a cooling chamber or any device or method for maintaining the samples in a frozen condition during the coring process. As such, the Applicant respectfully requests reconsideration and allowance of claims 1-4, 7-15 and 35-65.

Support for these amendments is found throughout the Applicant's specification:

As shown in Figure 2, the frozen tissue microarrayer device comprises at least one platform 12 moveable in an x or y direction relative to a fixed horizontal surface 1 and a **cooling chamber** 7 for receiving at least one frozen material (e.g., such as a donor block or a recipient block/microarray block) and for maintaining the frozen material in a frozen condition. Preferably, the **cooling chamber** 7 is moveable with the platform 12, such that when the platform 12 moves in an x-direction, the **cooling chamber** 12 also moves in an x- direction and when the platform moves in a y-direction, the **cooling chamber** 7 moves in a y-direction. (Specification; Page 22, Line 24-Page 23, Line 3)(Emphasis added).

The **cooling chamber** 7 can be cooled in a variety of ways, e.g., by providing the **cooling chamber** 7 with a source of cold water (e.g., water cooled to 1°C to 4°C), a mixture of cold water and ice, or compressed air. In one aspect, the **cooling chamber** 7 comprises sealed tubing configured to form a jacket of cooling fluid (e.g., water or air) around a block of frozen material. An insulator sheet (not shown) also can be placed between the platform 12 and **cooling chamber** 7, to minimize heat dissipation from the **cooling chamber** or heat conduction from the platform 12. In another aspect, the **cooling chamber** 7 further comprises a retaining chamber 6 for retaining at least one block of frozen material. The retaining chamber 6 is preferably made of an insulating material for maintaining a temperature of from 0°C to 4°C or below. In some aspects, the retaining chamber 6 is surrounded by cold water, a mixture of ice and water, or cold air (e.g., from a compressed air source which communicates with the cooling chamber 7), or a jacket through which a cooling fluid circulates. (Specification; Page 23, Lines 4-15)(Emphasis added).

> In one aspect, the movement of the retaining chamber 6 is coupled to that of the **cooling chamber** 7 which is turn is coupled to movement of at least one platform 12. The movement of the platform 12 can be controlled manually, e.g., by using a grasping element 12g (e.g., such as a joystick) coupled the platform 12, or can be mechanically controlled, e.g., by providing a motor in communication with the platform 12. In one aspect, an x-direction platform 12 in communication with an x-direction motor is provided for controlling movement of the cooling chamber 7 in an x-direction, and a y-direction platform 12 in communication with a y-direction motor is provided for controlling movement of the **cooling chamber** 7 in a y-direction. By providing both platforms, the **cooling chamber** 7 is able to move in both an x- and y- direction. (Specification; Page 26, Lines 10-18)(Emphasis added).

> In still a further aspect, a donor block is kept cooled within an insulated **cooling chamber** 7d outside of the device while the recipient block is processed in a **cooling chamber** 7. The **cooling chamber** 7 can then be removed from the device while **cooling chamber** 7d is seated on platform 12 for processing the donor block. (Specification; Page 28, Line 27-Page 29, Line2)(Emphasis added).

As shown by the above-identified passages, the Applicant has disclosed a tissue microarrayer with a cooling chamber to overcome various difficulties associated with utilizing samples that have been preserved with a frozen embedding material (i.e., maintaining the donor block and recipient block in a frozen condition during the coring process). As such, the Applicant's amended independent claim 1, amended independent claim 12 and all depending claims overcome the Office Action's §103 rejections as the cited references do not disclose, teach or suggest the element of a cooling chamber. The Applicant respectfully requests reconsideration and allowance of claims 1-4, 7-15 and 35-65.

As outlined in the above-passages from the Office Action, Leighton discloses a tissue microarrayer capable of creating a microarray from a paraffin starting material. Although Leighton does include a general statement that the Leighton tissue microarrayer is not limited to paraffin, Leighton **DOES NOT** teach, suggest, or disclose a method of adapting the tissue microarrayer to overcome the problems associated with coring frozen samples. More specifically, the Leighton invention **DOES NOT** disclose, teach or suggest the use of a cooling chamber to maintain the samples in a frozen condition during the coring process. As such, the Applicant's amended independent claim 1, amended independent claim 12 and all depending claims overcome the Office Action's §103 rejections as the cited references do not disclose,

teach or suggest the element of a cooling chamber. The Applicant respectfully requests reconsideration and allowance of claims 1-4, 7-15 and 35-65.

The Office Action cited Irving et al. as a cure to the deficiency of the Leighton reference. Irving et al. simply discloses that tissue and cell samples may be preserved by embedding the samples in a frozen material. Irving et al. **DOES NOT** teach, suggest, or disclose a method of adapting a tissue microarrayer to overcome the problems associated with coring frozen samples. Utilizing frozen samples by specifically adapting a tissue microarrayer is a novel solution to an existing problem of maintaining a sample in a frozen condition during a coring process. Neither Leighton nor Irving et al., alone or in any combination, disclose, teach or suggest the use of a cooling chamber to maintain the samples in a frozen condition during the coring process. Further, the cited references **DO NOT** address the difficulty of utilizing a frozen sample with a tissue microarrayer. As such, the Applicant's amended independent claim 1, amended independent claim 12 and all depending claims overcome the Office Action's §103 rejections as the cited art does not disclose, teach or suggest the element of a cooling chamber. The Applicant respectfully requests reconsideration and allowance of claims 1-4, 7-15 and 35-65.

The Office Action also rejected claims 1-15 and 35-65 under §103 to Leighton in view of Goldsworthy et al. (Mol. Carcinog (1999) 25(2): 86-91). Goldsworthy et al. simply discloses that tissue and cell samples may be preserved by embedding the samples in a frozen material. Neither Leighton nor Goldsworthy et al., alone or in any combination, teach, suggest or disclose a device or method of adapting a frozen tissue microarrayer so that frozen samples may be utilized. More specifically, neither Leighton nor Goldsworthy et al., alone or in any combination, teach, suggest, or disclose a tissue microarrayer comprising a cooling chamber as is claimed in amended independent claim 1 and amended independent claim 12. As such, the Applicant respectfully requests reconsideration and allowance of pending claims 1-4, 7-15, and 35-65.

In summary, neither Leighton, Irving et al., nor Goldsworthy et al., alone or in any combination, teach, suggest or disclose a device or method of adapting a frozen tissue microarrayer so that frozen samples may be utilized. More specifically, neither Leighton, Irving

et al., nor Goldsworthy et al., alone or in any combination, teach, suggest, or disclose a tissue microarrayer comprising a cooling chamber as is claimed in amended independent claim 1 and amended independent claim 12. As such, the Applicant respectfully requests reconsideration and allowance of pending claims 1-4, 7-15, and 35-65.

Kallioniemi et al. in view of Irving et al. and/or Goldsworthy et al.:

~~The Office Action rejected claims 1-15 and 35-65 under 35 U.S.C. §103(a) as being~~ unpatentable over U.S. Published Patent Application 2002/0132246 to Kallioniemi et al., in view of Irving et al. Similar to the discussion above regarding Leighton, Kallioniemi et al. discloses a tissue microarrayer capable of creating a microarray from a paraffin starting material. Although Kallioniemi et al. includes a general statement that the Kallioniemi et al. tissue microarrayer is not limited to paraffin, Kallioniemi et al. **DOES NOT** mention frozen tissue and/or cells and more importantly, Kallioniemi et al. **DOES NOT** teach, suggest, or disclose a method of adapting a tissue microarrayer to overcome the problems associated with coring frozen samples. More specifically, Kallioniemi et al. **DOES NOT** disclose, teach, or suggest the use of a cooling chamber to maintain the samples in a frozen condition during the coring process. As such, the Applicant's amended independent claim 1, amended independent claim 12, and all depending claims overcome the Office Action's §103 rejection as the cited references do not disclose, teach or suggest the element of a cooling chamber. The Applicant respectfully requests reconsideration and allowance of claims 1-4, 7-15 and 35-65.

The Office Action also rejected claims 1-15 and 35-65 under §103 to Kallioniemi et al in view of Goldsworthy et al. Parallel to the above-discussion, Irving et al. and Goldsworthy et al. simply disclose that tissue and cell samples may be preserved by embedding the samples in a frozen material. Irving et al. and Goldsworthy et al. **DO NOT** teach, suggest, or disclose a method of adapting a tissue microarrayer to overcome the problems associated with coring frozen samples. Utilizing frozen samples by specifically adapting a tissue microarrayer is a novel solution to an existing problem of maintaining a sample in a frozen condition during a coring process. Neither Kallioniemi et al., Irving et al., nor Goldsworthy et al., alone or in any combination, disclose, teach or suggest the use of a cooling chamber to maintain the samples in a frozen condition during the coring process. Further, the cited references **NEVER** address the

difficulty of utilizing a frozen sample with a tissue microarrayer. **The Applicant has addressed the problem and presented a solution.** As such, the Applicant's amended independent claim 1, amended independent claim 12, and all depending claims overcome the Office Action's §103 rejections as the cited references **DO NOT** disclose, teach or suggest the element of a cooling chamber. The Applicant respectfully requests reconsideration and allowance of pending claims 1-4, 7-15 and 35-65.

Conclusion:

In summary, the cited art of Leighton and Kallioniemi et al. each disclose a tissue microarrayer designed to be utilized with tissue and/or cell samples preserved in paraffin or "other materials." Neither Leighton nor Kallioniemi et al. address or suggest that their respective tissue microarrayers have been adapted to overcome the difficulties associated with utilizing frozen samples (i.e., maintaining samples in a frozen condition during the coring process). More specifically, neither Leighton nor Kallioniemi et al. disclose a tissue microarrayer comprising a cooling chamber (as recited in amended independent claim 1 and amended independent claim 12). As such, neither Leighton nor Kallioniemi et al. suggest, teach or make obvious the Applicant's amended claimed invention.

In addition, neither Irving et al. nor Goldsworthy et al. cure the deficiencies of the Leighton and/or Kallioniemi et al. references. Irving et al. and Goldsworthy et al. merely disclose that tissue and cells may be preserved by freezing. The ability to utilize frozen samples with a tissue microarrayer has met with difficulties. The Applicant's invention has addressed these difficulties (i.e., maintaining a frozen condition during the coring process and coring a frozen sample) and has presented a tissue microarrayer that presents a solution to these difficulties—the addition of a cooling chamber allows a sample to remain frozen during a coring process. Neither Leighton, Kallioniemi et al., Irving et al. nor Goldsworthy et al., alone or any combination, provide the motivation to address the difficulties of utilizing a frozen sample with a tissue microarrayer. Additionally, neither Leighton, Kallioniemi et al., Irving et al. nor Goldsworthy et al., alone or any combination, provide the motivation to combine a cooling chamber with a tissue microarrayer to enable a frozen sample to be utilized with the tissue

microarrayer. As amended with this response, no combination of Leighton, Kallioniemi et al., Irving et al., and Goldsworthy et al. disclose, teach, or make obvious pending claims 1-4, 7-15 and 35-65. Applicant's respectfully request reconsideration and allowance of pending claims 1-4, 7-15 and 35-65.

With this Amendment, Applicant has made an earnest effort to respond to all issues raised in the Final Office Action of, July 11, 2003, and to place all claims presented in condition for allowance. No amendment made was for the purpose of narrowing the scope of any claim, unless Applicant has argued herein that such amendment was made to distinguish over a particular reference or combination of references.

Applicant submits that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention.

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Respectfully submitted,

Date: September 10, 2003

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